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NEWS	4	Feb 16	TOXLINE no longer being updated
NEWS	5	Apr 23	Search Derwent WPINDEX by chemical structure
NEWS	6	Apr 23	PRE-1967 REFERENCES NOW SEARCHABLE IN CAPLUS AND CA
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=> s diacerein/cn

L1 1 DIACEREIN/CN

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L1 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2001 ACS
RN 13739-02-1 REGISTRY
CN 2-Anthracenecarboxylic acid, 4,5-bis(acetyloxy)-9,10-dihydro-9,10-dioxo- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 2-Anthroic acid, 9,10-dihydro-4,5-dihydroxy-9,10-dioxo-, diacetate (8CI)
CN Rhein, diacetate (6CI)
OTHER NAMES:
CN 1,8-Diacetoxy-3-carboxyanthraquinone
CN 4,5-Diacetoxyanthraquinone-2-carboxylic acid
CN 4,5-Diacetylrhein
CN **Diacerein**
CN Diacerhein
CN Diacetylrhein
FS 3D CONCORD
MF C19 H12 O8
CI COM
LC STN Files: ADISINSIGHT, AGRICOLA, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CHEMCATS, CHEMLIST, CIN, CSCHEM, DDFU, DRUGNL, DRUGPAT, DRUGU, DRUGUPDATES, EMBASE, IPA, MEDLINE, MRCK*, NAPRALERT, PHAR, PROMT, RTECS*, SYNTHLINE, TOXLINE, TOXLIT, USAN, USPATFULL
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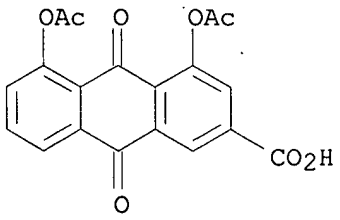

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63 REFERENCES IN FILE CAPLUS (1967 TO DATE)
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L2 1 RHEIN/CN

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L2 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2001 ACS
RN 478-43-3 REGISTRY
CN 2-Anthracenecarboxylic acid, 9,10-dihydro-4,5-dihydroxy-9,10-dioxo- (9CI)
(CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 2-Anthraquinonecarboxylic acid, 4,5-dihydroxy- (6CI)
CN 2-Anthroic acid, 9,10-dihydro-4,5-dihydroxy-9,10-dioxo- (8CI)
OTHER NAMES:
CN 1,8-Dihydroxy-3-carboxyanthraquinone
CN 1,8-Dihydroxyanthraquinone-3-carboxylic acid
CN 4,5-Dihydroxy-2-anthraquinonecarboxylic acid
CN Cassic acid
CN Chrysazin-3-carboxylic acid
CN Monorhein
CN Rheic acid
CN **Rhein**
CN Rhubarb yellow
FS 3D CONCORD
MF C15 H8 O6
CI COM
LC STN Files: ANABSTR, BEILSTEIN*, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAOLD,
CAPLUS, CASREACT, CHEMCATS, CHEMINFORMRX, CHEMLIST, CSCHEM, DDFU, DRUGU,
EMBASE, HODOC*, IPA, MEDLINE, MRCK*, NAPRALERT, RTECS*, SYNTHLINE,
TOXLINE, TOXLIT, USPATFULL
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Other Sources: EINECS**
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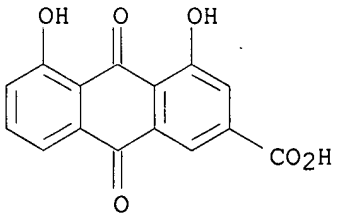

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14 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
389 REFERENCES IN FILE CAPLUS (1967 TO DATE)
20 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

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=> s autoimmune disease or inflammat?

L3      811435 AUTOIMMUNE DISEASE OR INFLAMMAT?

=> s rheumatoid arthritis or psoriatic arthritis or asthma or Wegener's
disease or emphysema or Paget's disease or osteoporosis or bone metastases or
atherosclerosis or myeloma or myeloid leukemia

   2 FILES SEARCHED...
L4      720864 RHEUMATOID ARTHRITIS OR PSORIATIC ARTHRITIS OR ASTHMA OR
WEGENER
               'S DISEASE OR EMPHYSEMA OR PAGET'S DISEASE OR OSTEOPOROSIS OR
               BONE METASTASES OR ATHEROSCLEROSIS OR MYELOMA OR MYELOID
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L6         171 L4 AND L5

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L7         145 L3 AND L6

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   4 FILES SEARCHED...
L8         134 L7 AND PY<2000

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L9           7 L8 AND INTERLEUKIN-1

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L10  ANSWER 1 OF 7  USPATFULL
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SUMM . . . decreased production and/or function of immunoinhibitory mediators, especially cytokines, and/or is related to an increased production and/or function of certain immuno-**inflammatory** mediators, especially cytokines. In particular, the invention relates to the use of a substance of the invention for the manufacture of a pharmaceutical composition for prevention and/or treatment of auto-immune diseases (diabetes mellitus, type I; **inflammatory** diseases of the gastro-intestinal tract; **rheumatoid arthritis**), arthritis urica (gout), allergy of the skin; allergic reactions in the skin, lungs and respiratory tract (including **asthma** bronchiale); tissue damage as a result of hypoxia/ischemia (infarction; reperfusion); **atherosclerosis**; psoriasis; granulomatous disease; chronic myeloid leukaemia; acute myeloid leukaemia; cancer; graft vs. host reaction and conditions related to transplant rejection; fibrosis of the lung; fibrosis of the liver; chronic non-infectious **inflammation** of the lung; glomerulonephritis; pre-term labour; periodontitis; **inflammatory** reactions due to virus infections, **osteoporosis**, septic shock and/or for the manufacture of an anti-conceptive agent.

SUMM Research from the last two decades has shown that the initiation, regulation and ending of **inflammatory** reactions as well as the regulation of growth and differentiation within the mammalian organisms is under tight control by a. . . key factors for the development of cellular immune reactions, which in turn form the basis for the clinical manifestations of **inflammation** due to infection, allergy, trauma, graft vs. host reactions and auto-immune diseases. The allergic and auto-immune diseases are explained by. . . etiology. In vitro studies, animal experiments and clinical experimental studies have shown that cytokines play important pathophysiological roles for the **inflammatory** reactions related to auto-immune diseases, allergy, ischemia, reperfusion injury, trauma, infections, and are important for the development of cancer, **atherosclerosis**, pregnancy and fetal development, bone homeostasis. Cytokines may be involved in other immunoinflammatory and proliferative diseases as will be described. . .

SUMM . . . and immortalized B cells, and in addition to its cytokine synthesis inhibitory factor (CSIF) activity, inhibiting the production of several pro-**inflammatory** cytokines and colony-stimulating factors, it also induces the production of a natural **interleukin -1** receptor antagonist protein/peptide (IRAP) by mono-nuclear cells, thereby indirectly inhibiting IL-1 activity. IL-10 also downregulates its own production by monocytes. . .

SUMM . . . vIL-10 for the manufacture of a pharmaceutical composition for the treatment of various conditions such as septic or toxic shock, **rheumatoid arthritis**, graft-vs-host disease, tissue rejection, diabetes mellitus, autoimmune disorders, leukaemia and cancer has been disclosed in e.g. WO93/02693 and WO94/04180. Moreover,. . .

SUMM c) induces production of **interleukin-1** receptor antagonistic protein (IRAP) by human monocytes,

SUMM . . . homology to hIL-10, called IT9302), and derivatives thereof can be used for the prevention and/or treatment of certain forms of **inflammatory** processes, especially forms related to the immune and/or hormone system. It is contemplated (as described in detail in the following. . .

SUMM The cellular immune system takes part in the development of such disorders as infectious, **inflammatory** and neoplastic diseases. Immunocompetent cells and their products may play important roles in the

initiation, progression and possible chronic nature of development of **inflammatory** conditions. These disorders are often without known etiology and includes common diseases such as diabetes mellitus, **rheumatoid arthritis**, **inflammatory** diseases of the gastro-intestinal tract and of the skin. Apart from these examples, cell-mediated immunity or pro-**inflammatory** mediators, however, contribute to many other **inflammatory** and proliferative diseases (see Table 2).

SUMM . . . are considered pathogenetically important

Skin diseases:
Psoriasis
Atopic dermatitis
Contact dermatitis
Cutaneous T cell lymphoma (CTCL)
Sezary syndrome
Pemphigus vulgaris
Bullous pemphigoid
Erythema nodosum
Scleroderma
Auto-immune (including rheumatic) diseases:
Uveitis
Bechet's disease
Sarcoidosis Boeck
Sjogren's syndrome
Rheumatoid arthritis
Juvenile arthritis
Reiter's syndrome
Gout
Osteoarthrosis
Systemic lupus erythematosis
Polymyositis
Myocarditis
Primary biliary cirrhosis
Crohn's disease
Ulcerative colitis
Multiple sclerosis and other demyelinating diseases
Aplastic anaemia
Idiopathic thrombocytopenic purpura
Multiple **myeloma** and B cell lymphoma
Simmons' panhypopituitarism
Graves' disease and Graves' opthalmopathy
Subacute thyreoditis and Hashimoto's disease
Addison's disease
Insulin-dependent diabetes mellitus (type 1)
Other diseases
Various clinical syndromes with vasculitis (e.g. polyarteritis nodosa, Wegener's granulomatosis, Giant cell arteritis
Fever, malaise
Anorexia (e.g. in acute and chronic **inflammatory** and infectious diseases)
Disseminated intravascular coagulation (DIC)
Arteriosclerosis (**atherosclerosis**)
Shock (e.g. in gram-negative sepsis)
Cachexia (e.g. in cancer, chronic infectious and chronic **inflammatory** diseases)
Transplant rejection and graft vs. host disease

SUMM . . . also explain while tagging failed to show missing functions. Recombinant mIL-10 and hIL-10 have been expressed in: CDS7 cells, mouse **myeloma** cells, chinese hamster ovary cells, a baculovirus expression system, and E. coli. The biological activities of these rIL-10 proteins are. . .

SUMM . . . monocytes to migrate as a response to the chemokine MCP-1/MCAF (75). Further, hIL-10 induces the production of an endogenous, natural **interleukin-1** receptor antagonist (IRAP) (6), which

inhibits IL-1.alpha. and IL-1.beta. by competing with receptor binding. Since IL-8 is strongly inducible by. . . This last mechanism is of considerable importance for the present invention as described and exemplified in the following. IRAP has anti-**inflammatory** activities (9), and its therapeutic effect in **rheumatoid arthritis** has been suggested (10). Also, IRAP proved to be effective in the treatment of sepsis syndrome and a dose-dependent, 28-day. . . was associated with IRAP treatment (p=0.015) in a study by Fisher et al. (11). IRAP may exert parts of its anti-**inflammatory** effects by inhibiting chemokine-production such as the production of IL-8.

SUMM . . . where an enhanced cell-mediated immunoreactivity is believed to play a role for the disease, such as in auto-immune diseases and **inflammation**. Anti-IL-10 antibody-treated mice show a stronger **inflammatory** response to monokine-induced **inflammation** and are significantly more susceptible to death induced by LPS-induced septic shock, a monokine-mediated **inflammatory** reaction (16). Also, IL-10 knock-out mice spontaneously develop **inflammatory** reactions of the gut similar to that of colitis ulcerosa (17). Additionally, it has been investigated whether IL-10 plays a. . .

SUMM These in vivo results/data strongly suggest a homeostatic role of IL-10 in controlling cell-mediated and monokine-amplified immune **inflammation** and indicate the wide-ranged therapeutical applications of IL-10 or a drug with IL-10-like activity in the treatment of diseases which. . .

SUMM . . . induction of IRAP production and/or inhibition of cytokine-production and/or activity may have therapeutic importance (ref. 20-74)

Pre-term labour caused by infection or other conditions
Rheumatoid arthritis
Lyme's arthritis
Gout
Sepsis syndrome
Hyperthermia
Ulcerative colitis or enterocolitis
Osteoporosis
Cytomegalovirus
Periodontal diseases
Glomerulonephritis
Chronic, non-infectious **inflammation** of the lung (e.g. sarcoidosis and smoker's lung)
Granuloma formation
Fibrosis of the liver
Fibrosis of the lung
Transplant rejection
Graft vs. host disease
Chronic myeloid leukaemia
Acute myeloid leukaemia
Other neoplastic diseases
Asthma bronchiale
Diabetes mellitus, type I (insulin dependent)
Arteriosclerosis/**atherosclerosis**
Psoriasis
Chronic B lymphocyte leukaemia
Common variable immunodeficiency
Side-effects using other biological response modifiers
Disseminated intravascular coagulation
Systemic sclerosis
Encephalomyelitis
Lung **inflammation**
Hyper IgE syndrome
Enterocolitis
Cancer metastasis and growth
Adoptive immune therapy

Acquired respiratory distress syndrome
Sepsis
Reperfusion syndrome
Postsurgical **inflammation**
Organ transplantation
Alopecia

SUMM c) induces production of **interleukin-1** receptor antagonistic protein (IRAP) by human monocytes,

DETD . . . IL-8) was a kind gift from Dainippon Pharmaceuticals Co. Ltd., Osaka, Japan), and IFN-.gamma. was purchased from Boehringer Ingelheim Am **Rhein**, Germany. To obtain specific inhibition of IL-8 stimulation, a neutralizing monoclonal anti-IL-8 antibody (WS.4) was used (a kind gift from. . .

DETD IT9302 Induced Production of **Interleukin-1** Receptor Antagonist Protein (IRAP) by Human Monocytes

DETD The present data demonstrate a dose-dependent inhibitory effect of the synthetic nonapeptide, IT9302, on processes which reflect pro-**inflammatory** activity, including IL-8 production and monocyte and/or T cell migration. Thus, IT9302 was able to suppress the spontaneous production of. . . of CD4+ T cells to migrate as a response to IL-8. Since IL-8 is related to many different states of **inflammation** and since CD4+ T cells appear early in the infiltrate of T cell-mediated immune **inflammation** such as allergy of the skin, this feature may prove to have significant therapeutic value for the control of T cell-mediated immune **inflammation**.

DETD . . . IL-10, and IT9302 may thus activate T cell populations with suppressor activity contributing to the ending of T cell-mediated immune **inflammation**. Therefore IT9302 according to the examples which are demonstrated above, possesses therapeutic value in diseases where IL-10 and/or IRAP may. . .

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DETD . . . van Leeuwen, P. A. M., Schneider, A. J., Houdijk, A. P. J., Ferwerda, C. C., Wesdorp, R. I. C. 1993. **Interleukin-1** receptor antagonist: A new therapeutic agent in the treatment of septic syndrome. Ned. Tijdschr. Geneesks. 137/7: 337-342

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DETD . . . R. C., Panara, M. R., Reale, M., Placido, F. C., Eridas, S.,

Bongrazio, M., Dempsey, R. A. 1992. Human recombinant **interleukin-1** receptor antagonist (hrIL-1ra) enhances the stimulatory effect of interleukin-2 on natural killer cell activity against MOLT-4 target cells. Int. J.. . .

DETD 69. Selig, W., Tocker, J. 1992. Effect of **interleukin-1** receptor antagonist on antigen-induced pulmonary responses in guinea pigs. Eur. J. Pharmacol. 213/3: 331-336

DETD . . . S., Neben, S., Newman, G., Sieff, C., Thompson, R. C., Burakoff, S. J., Ferrara, J. L. M. 1991. Inhibition of **interleukin-1** by an **interleukin-1** receptor antagonist prevents graft-versus-host diseases.Blood 78/8: 1915-1918

DETD . . . Kantarjian, H., Blake, M., Harris, D., Gutterman, J. U., Talpaz, M. 1991. Suppression of chronic myelongenous leukemia colony growth by **interleukin-1** (IL-1) receptor antagonist and soluble IL-1 receptors: A novel application for inhibitors of IL-1 activity. Blood 78/6: 1476-1484

DETD . . . J., Chesonis, R. S., Pignatello, M., Schmolze, D., Symington, J., Kilin, P. L., Thompson, R. C. 1991. Evaluation of an **interleukin-1** receptor antagonist in the rat acetic acid-induced colitis model. Agents Actions 34/1-2: 187-190

DETD . . . Neely, H. A., Reardon, I. M., Heinrikson, R. L. et al. 1990. Purification, cloning expression and biological characterization of an **interleukin-1** receptor antagonist protein. Nature 344/6267:633-638

CLM What is claimed is:

. . . human monocytes, (b) induces inhibition of IL-1.beta. induced IL-8 production by human peripheral blood mononuclear cells, (c) induces production of **interleukin-1** receptor antagonistic protein (IRAP) by human monocytes, (d) induces chemotactic migration of CD8.sup.+ human T lymphocytes in vitro, (e) desensitizes. . .

. . . human monocytes, (b) inducing inhibition of IL-1.beta. induced IL-8 production by human peripheral blood mononuclear cells, (c) inducing production of **interleukin-1** receptor antagonistic protein (IRAP) by human monocytes, (d) inducing chemotactic migration of CD8.sup.+ human T lymphocytes, (e) desensitizing human CD8.sup.+. . .

. . . 35, wherein said patient is afflicted with a disorder selected from the group consisting of pre-term labour caused by infection, **rheumatoid arthritis**, Lyme's arthritis, gout, sepsis syndrome, hyperthermia, ulcerative colitis, enterocolitis, **osteoporosis**, cytomegalovirus, periodontal disease, glomerulonephritis, chronic non-infectious **inflammation** of the lung, sarcoidosis, smoker's lung, granuloma formation, fibrosis of the liver, fibrosis of the lung, transplant rejection, graft vs. host disease, chronic **myeloid leukemia**, acute **myeloid leukemia**, neoplastic diseases, **asthma** bronchiale, type I insulin dependent diabetes mellitus, arteriosclerosis, **atherosclerosis**, psoriasis, chronic B lymphocyte leukaemia, common variable immunodeficiency, disseminated intravascular coagulation, systemic sclerosis, encephalomyelitis, lung **inflammation**, hyper IgE syndrome, cancer metastasis, cancer growth, adoptive immune therapy, acquired respiratory distress syndrome, sepsis, reperfiision syndrome, postsurgical **inflammation**, organ transplantation, and alopecia.

AN 2000:167984 USPATFULL|

TI Immunomodulators|

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Gesser, Borbala, Hasselager, Denmark

PA Steeno Research Group A/S, Odense, Denmark (non-U.S. corporation)

PI US 6159937 20001212
WO 9601318 19960118 <--

AI US 1997-765094 19970106 (8)
WO 1995-DK227 19950607

19970102 PCT 371 date
19970102 PCT 102(e) date
PRAI DK 1994-800 19940705
DT Utility|
FS Granted|
EXNAM Primary Examiner: Kemmerer, Elizabeth; Assistant Examiner: Romeo, David S.|
LREP Cooper, Iver P.|
CLMN Number of Claims: 44|
ECL Exemplary Claim: 1|
DRWN 13 Drawing Figure(s); 11 Drawing Page(s)|
LN.CNT 2309|
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L10 ANSWER 2 OF 7 USPATFULL
PI US 5989594 19991123 <--
DETD . . . incidence of alopecia, achromotrichia, encephalomyopathy, spontaneous fractures, aneurysms, and paresis. This syndrome bears a remarkable similarity to aflatoxin poisoning. Chronic **inflammation** of the small intestine is apparent at necropsy (unpublished). This chronic **inflammation** is not exclusive to this disorder, it is so common as to be misconstrued as normal (5).
DETD . . . the ostrich and rhea, is characterized by extreme weight loss and muscle degeneration, lethargy, hypothermia, decreased appetite, stunting, frequent intestinal **inflammation**, ascites, and death, usually within the first month with or without secondary infections (6).
DETD . . . birds share two common disease symptoms: extreme muscle degeneration and adipose depletion. Prior reports suggest the adipose has anecdotal topical anti-**inflammatory** activity in humans (17-22), and compromised rhea chicks were successfully treated with adipose replacement therapy by intraperitoneal injection (23).
DETD . . . bone extract appropriate for humans and other animals. As shown in FIG. 2, toxins play a pivotal role in the **autoimmune diseases** as well as immune function and the muscle and bone extract can be used to detoxify affected individuals and animals.
DETD . . . of these chicks can be directly traced back to their unique immune systems that rely not only on a bioactive, anti-**inflammatory** body fat, but muscle components critical to their immune system function:
DETD . . . may lead to a loss of cell viability and to cell necrosis and could initiate the skeletal muscle damage and **inflammation** caused by exhaustive exercise (38).
DETD . . . may be a mechanism evolved to efficiently dispose of the free proteins released in the proteolytic process of accessing the anti-**inflammatory**, immune system, and calcium regulatory proteins, phospholipids, and energy components.
DETD . . . likely cytokines mediate the fatal muscle wasting just as they do in humans and other animals. Tumor necrosis factor (TNF), **interleukin-1** (IL-1), interleukin-6 (IL-6), interferon-gamma (IFN-gamma), and differentiation factor (D-factor) are thought to play a part in the pathophysiology of cancer. . .
DETD 3. regulators of immune-mediated **inflammation** which activate non-specific **inflammatory** cells elicited in response to specific antigen recognition by T lymphocytes,
DETD Cytokines include tumor necrosis factor, interleukins, chemokines, and transforming growth factors. Cytokines mediate such diverse responses as cachexia, fever, **inflammation**, growth regulation, antiviral activity, antibody synthesis and activation inhibition, acting on T cells and natural killer cells, various blood cells,. . . as the liver, thymus, hypothalamus, muscle and fat. These proteins are important mediators in natural immunity, acute response, immune mediated **inflammation**, hematopoiesis (growth and differentiation of bone

marrow progenitor cells) and regulation of lymphocyte activation, growth, and control (99).

DETD . . . are affected by degeneration or malfunction of the cytokine system include Crohn's disease, AIDS, Epstein-Barr and other chronic viral infections, **autoimmune diseases** including **rheumatoid arthritis**, dermatomyositis, lupus erythematous, ulcerative colitis, atrophic gastritis, thyroiditis, aging, drug-induced immunodeficiency caused by corticosteroids, anticancer drugs, radiotherapy, or transplant immunosuppressive drugs, advanced cancers, lymphocytic leukemia, multiple **myeloma**, Hodgkin's disease, iron deficiency, and protein-calorie malnutrition (100). These disorders may show improvement by regular supplementation with the bioactive proteins. . .

DETD This example shows the effectiveness of the extract in the treatment of petrochemicals poisoning and Crohn's disease, **inflammatory** bowel disease, or colitis. The named disorders share one thing in common: chronic diarrhea. Rhea Extract relieves the diarrhea and. . .

DETD This example demonstrates the use of rhea extract in the treatment of colitis, **inflammatory** bowl disease, Crohn's disease, diarrhea, gastric ulcers.

DETD . . . This pathway would compete for sulfation of the heparan sulfate present in the basement membrane of the intestinal tract. Intestinal **inflammation** and diarrhea is a common problem in infant ostriches, rheas, and pigs. It has been speculated that soybean meal may. . .

DETD 134. Yamauchi K, Yagi T, Kuwano S. Suppression of the purgative action of **rhein** anthrone, the active metabolite of sennosides A and B, by calcium channel blockers, calmodulin antagonists and indomethacin. Pharmacology 1993;47(Suppl 1):22-31.

AN 1999:150697 USPATFULL

TI Ratite extracts as therapeutic agents

IN Cardinale Fezler, Donna L., Rte. 1, Box 97B, Jacksonville, IL, United States 62650

PI US 5989594 19991123 <--

AI US 1997-907794 19970808 (8)

PRAI US 1996-24152 19960809 (60)

DT Utility

FS Granted

EXNAM Primary Examiner: Witz, Jean C.

LREP Fishel, Grace J.

CLMN Number of Claims: 6

ECL Exemplary Claim: 1

DRWN 2 Drawing Figure(s); 2 Drawing Page(s)

LN.CNT 2214

L10 ANSWER 3 OF 7 USPATFULL

PI US 5962424 19991005 <--

DETD . . . treated with 80 to 90 Gy, 44% fail within the field of irradiation (Fletcher and Shukovsky, 1975). Furthermore, 50% of **inflammatory** breast carcinoma patients have local recurrences when the treated with daily irradiation (Barker et al., 1980), while twice daily irradiation. . .

DETD The findings that acute and subacute clinical manifestations of ionizing radiation may in part mimic the **inflammatory** response to a number of stimuli (Slauson et al., 1976; Narayan and Cliff, 1982; Dunn et al., 1986) prompted the. . . al., 1990; Hopewell et al., 1993; Dunn et al., 1986; Matzner et al., 1988). One of the components of acute **inflammation** is enhanced adherence of leukocytes to the endothelium before extravasation (Cliff, 1966). During the **inflammatory** reaction, endothelial cells rapidly and transiently produce a number of glycoproteins that influence neutrophil binding (Pober and Cotran, 1990).

DETD . . . ICAM increased from 20 to 30% in untreated controls to 50 to 65% at 20 h following irradiation. In comparison, **interleukin-1** was used as a positive control and increased the expression of each of the adhesion molecules by 20 fold for. . .

DETD The acute and subacute clinical manifestations of ionizing radiation mimic the **inflammatory** response to a number of stimuli. For example, radiation-induced pneumonitis, cystitis, mucositis, esophagitis and dermatitis each demonstrate **inflammation** as a predominant component (Slauson et al., 1976; Dunn et al., 1986; Ward et al., 1993). Furthermore, ionizing radiation is associated with neutrophilic vasculitis and interstitial **inflammation** (Narayan, 1982; Slauson et al., 1976; Fajardo and Berthrong, 1988).

DETD Endothelial cells exposed to ionizing radiation respond in a manner analogous to that observed during acute **inflammation**. This response is associated with leukocyte margination and an increase in vascular permeability. These processes may account for the pathogenesis of radiation injury (Hopewell et al., 1993). An understanding of the pathophysiology of the radiation-mediated **inflammatory** response will facilitate pharmacologic intervention for these sequelae of radiation therapy.

DETD Endothelial cells rapidly and transiently produce a number of glycoproteins that influence neutrophil binding during the **inflammatory** reaction (Pober and Cotran, 1990). The potential pathology associated with expression of these proteins on the surface of the endothelium. . .

DETD . . . controlled (Montgomery et al., 1991; Ghersa et al., 1992) because of its pivotal role in the endothelial cell response during **inflammation** and hypoxia, whereas ICAM induction is regulated less vigorously. Due to the association between oxidant injury and the expression of. . .

DETD . . . 1A-4, FIG. 1A-5 and FIG. 1A-6). However, there was no significant increase in P-selectin or VCAM protein expression following irradiation. **Interleukin-1** (IL-1) as used as a positive control and shifted the log fluorescence for E-selectin by 43%, ICAM-1 (31%), VCAM-1 (25%),. . .

DETD Primary adhesion of leukocytes to the endothelium is an initial step in **inflammation** (Jones et al., 1995). To begin investigating this process in radiation-mediated **inflammation**, the inventors quantified adhesion molecules on endothelial cells after x-irradiation. The inventors found that E-selectin and ICAM-1 are induced by. . .

DETD . . . et al., 1993; Jones et al., 1995). Thus, x-ray-mediated CAM expression in endothelial cells may play a role in the **inflammatory** effects of ionizing radiation.

DETD . . . E-selectin and ICAM within endothelial cells. This is supported by the association of reactive oxygen species in the development of **atherosclerosis** (Collins, 1993) and renal injury from radiation (Jaenke et al., 1993). In this regard, endothelial cells are continuously exposed to. . . forms of reactive oxygen species. For example, H.sub.2 O.sub.2 and other oxygen radicals are produced by granulocytes and macrophages during **inflammation** and reoxygenation (Dowell et al., 1993).

DETD . . . ionizing radiation exposure. The inventors now propose that vascular injury within irradiated tissues occurs through the activation of a local **inflammatory** response mediated by adhesion molecules as well as cytokines (Hallahan et al., 1989). The clinical implication of these findings is. . . ligands (Nelson et al., 1993; Narasinga Rao et al., 1994) may be effective in the treatment or prevention of the **inflammatory** component of radiotherapy.

DETD . . . necessary for induction following stimulation with tumor necrosis factor (TNF) (Whelan et al., 1991). NFkB rapidly activates gene expression during **inflammation** and the immune response. The

NFkB motif in the E-selectin promoter (GGGGATTTCC; SEQ ID NO:1) is in agreement with the. . .

DETD If, in certain clinical environments, E-selectin induction is not highly specific and E-selectin is expressed in sites of **inflammation**, hypoxia or reoxygenation, pre-existing E-selectin sites will be blocked with glycerrhizin prior to irradiation and addition of E-selectin-second agent conjugates. . .

DETD The antibody-producing B lymphocytes from the immunized animal are then fused with cells of an immortal **myeloma** cell, generally one of the same species as the animal that was immunized. **Myeloma** cell lines suited for use in hybridoma-producing fusion procedures preferably are non-antibody-producing, have high fusion efficiency, and enzyme deficiencies that. . .

DETD Any one of a number of **myeloma** cells may be used, as are known to those of skill in the art (Goding, pp. 65-66, 1986; Campbell, pp.. . .

DETD One preferred murine **myeloma** cell is the NS-1 **myeloma** cell line (also termed P3-NS-1-Ag4-1), which is readily available from the NIGMS Human Genetic Mutant Cell Repository by requesting cell line repository number GM3573. Another mouse **myeloma** cell line that may be used is the 8-azaguanine-resistant mouse murine **myeloma** SP2/0 non-producer cell line.

DETD Methods for generating hybrids of antibody-producing spleen or lymph node cells and **myeloma** cells usually comprise mixing somatic cells with **myeloma** cells in a 2:1 proportion, though the proportion may vary from about 20:1 to about 1:1, respectively, in the presence. . .

DETD . . . does not pose a problem, as the viable, fused hybrids are differentiated from the parental, unfused cells (particularly the unfused **myeloma** cells that would normally continue to divide indefinitely) by culturing in a selective medium. The selective medium is generally one. . .

DETD . . . selection medium is HAT. Only cells capable of operating nucleotide salvage pathways are able to survive in HAT medium. The **myeloma** cells are defective in key enzymes of the salvage pathway, e.g., hypoxanthine phosphoribosyl transferase (HPRT), and they cannot survive. The. . . within about two weeks. Therefore, the only cells that can survive in the selective media are those hybrids formed from **myeloma** and B cells.

DETD . . . (often into the peritoneal cavity) into a histocompatible animal of the type that was used to provide the somatic and **myeloma** cells for the original fusion. The injected animal develops tumors secreting the specific monoclonal antibody produced by the fused cell. . .

DETD . . . for stability and to more closely approximate the original sLe.sup.x pharmacophore, resulted in an easily synthesized, effective selectin blocker with anti-**inflammatory** activity.

DETD . . . comparable to those of glycyrrhizin; .alpha.-Hederin, which showed a weaker activity, inhibiting at 2-3 mM concentrations; carmine; picrocarmine; carmine ammonia; **rhein**-8-glucoside; kasugamycin hydrochloride; kasugamycin; meglumine diatrizoate; [ring-.sup.14 C]Chlorhexidine; trigalacturonic acid; escin; metrizoic acid (meglumine salt); and N-(.alpha.-Rhamnopyranosyloxy hydroxyphosphonyl)-Leu-Trp (sodium salt). All. . .

DETD Glycyrrhizin is used in Chinese herbal medicines as an anti-**inflammatory** agent (Davis and Morris, 1991) and is therefore safe for human administration. The synthetic derivatives, especially the C-fucoside of glycyrrhetinic. . .

DETD . . . selectin-mediated cell adhesion. The human anticoagulant factor, Protein C, is a unique fucosylated plasma glycoprotein that has reported anti-ischemic and anti-**inflammatory** properties. It has been reported that both human plasma-derived and human cell-produced

recombinant Protein C inhibit E-selectin-mediated cell adhesion (Grinnell. . .

DETD . . . of memory T cells into certain skin lesions. Olofsson et al. (1994) also showed that E-selectin mediates leukocyte rolling in **interleukin-1**-treated rabbit mesentery venules.

DETD . . . example, Keelan et al. (1994a) have studied endothelial luminal surface expression of E-selectin in vivo in the pig. Here, intravenous **interleukin-1** (IL-1 infusion for 2 h) was used to induce E-selectin expression in various organs, as shown by immunostaining and selective. . .

DETD . . . activity in the inflamed knee in each of three animals. Radiolabeled anti-E-selectin Mab was thus successfully used to image localized **inflammatory** tissues (Keelan et al., 1994b).

DETD This approaches of Keelan et al. (1994a;b) to quantify changes in vascular luminal expression of E-selectin in models of **inflammation** and arthritis is considered as a suitable model for adaptation for analyzing E-selectin changes in relation to radiation treatment or. . .

DETD . . . phases of delayed hypersensitivity (DHR) resulted in IgG localization to dermal endothelium. The relative numbers of lymphocytes localized to the **inflammatory** site were significantly reduced in DHR modified with infusions of antibodies to E-selectin, while the numbers of lymphocytes recruited to. . .

DETD . . . also evaluated the expression of E-selectin on endothelium and epithelium in bronchial biopsies obtained from patients with allergic and non-allergic **asthma**. Bronchial biopsies were taken in asthmatic patients and control subjects (n=10) by fiberoptic bronchoscopy and embedded in paraffin. The cellular. . .

DETD This invention also provides compositions and methods for use in preventing or treating radiation-induced **inflammation** using E-selectin-based therapeutics in the absence of a second selected agent.

DETD Radiation is known to induce pneumonitis, cystitis, mucositis, esophagitis, dermatitis, neutrophilic vasculitis, acute pulmonary radiation injury and interstitial **inflammation** (Slauson et al., 1976; Dunn et al., 1986; Ward et al., 1993; Narayan, 1982; Fajardo and Berthrong, 1988; Hopewell et. . .

DETD . . . agents will be used as intravenous injections and oral preparations in phase I dose escalation trials to treat severe radiation **inflammation**, such as in the lung and pericardium.

DETD Barker et al., "Clinical experience of **inflammatory** breast carcinoma of the breast with or without chemotherapy," Cancer, 45:625-9, 1980.

DETD Brach et al., "Ionizing radiation stimulates NF-kB binding activity in human **myeloid leukemia** cells," J. Clin. Invest., 88:691-695, 1991.

DETD Cliff, "The acute **inflammatory** reaction in the rabbit ear chamber," J. Exp. Med., 124:546-556, 1966.

DETD Groves et al., "Endothelial leucocyte adhesion molecule-1 (ELAM-1) expression in cutaneous **inflammation**," Br J Dermatol, 124(2):117-23, 1991.

DETD Munro et al., "Expression of sialyl-Lewis X, an E-selectin ligand, in **inflammation**, immune processes, and lymphoid tissues," Am J Pathol, 141(6):1397-408, 1992

DETD Narasinga Rao et al., "Sialyl Lewis X mimics derived from a Pharmacophore search are selectin inhibitors with anti-**inflammatory** activity," J. Biol. Chem., 269:19663-19666; 1994.

DETD Olofsson et al., "E-selectin mediates leukocyte rolling in **interleukin-1**-treated rabbit mesentery venules," Blood, 84(8):2749-58, 1994.

DETD Saluson et al., "**Inflammatory** sequences in acute pulmonary radiation injury," 82:529-572, 1976.

DETD Slauson et al., "**Inflammatory** sequences in acute pulmonary

radiation injury," Am. J. Path., 82:549-572, 1976.
DETD Swerlick and Lawley, "Role of Microvascular Endothelial Cells in **Inflammation**," HDMEC In **Inflammation**, 100(1):111S-1115s, 1993.
DETD Ulich et al., "Intratracheal administration of endotoxin and cytokines: VIII. LPS induces E-selectin expression; anti-E-selectin and soluble E-selectin inhibit acute **inflammation**," **Inflammation**, 18(4):389-98, 1994.
DETD Veale et al., "Reduced synovial membrane macrophage numbers, ELAM-1 expression, and lining layer hyperplasia in **psoriatic arthritis** as compared with **rheumatoid arthritis**," Arthritis Rheum, 36(7):893-900, 1993.
AN 1999:121326 USPATFULL
TI Methods and compositions for targeting selectins
IN Hallahan, Dennis E., Park Ridge, IL, United States
Weichselbaum, Ralph R., Chicago, IL, United States
PA Arch Development Corporation, Chicago, IL, United States (U.S. corporation)
PI US 5962424 19991005 <--
AI US 1995-392541 19950221 (8)
DT Utility
FS Granted
EXNAM Primary Examiner: Campbell, Bruce R.; Assistant Examiner: Nguyen, Dave Trong
LREP Arnold, White & Durkee
CLMN Number of Claims: 25
ECL Exemplary Claim: 1
DRWN 8 Drawing Figure(s); 8 Drawing Page(s)
LN.CNT 3471
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L10 ANSWER 4 OF 7 USPATFULL
PI US 5916910 19990629 <--
AB . . . dithiocarbamates, or "DC") and pharmacologically active agents (e.g., NSAIDs). Invention conjugates provide a new class of pharmacologically active agents (e.g., anti-**inflammatory** agents) which cause a much lower incidence of side-effects due to the protective effects imparted by modifying the pharmacologically active. . .
SUMM . . . modern pharmaceutical technology, many drugs still possess untoward toxicities which often limit the therapeutic potential thereof.
For example, although non-steroid anti-**inflammatory** drugs (NSAIDs) are a class of compounds which are widely used for the treatment of **inflammation**, pain and fever, NSAIDs (e.g., aspirin, ibuprofen and ketoprofen) can cause gastrointestinal ulcers, a side-effect that remains the major limitation. . .
SUMM . . . expressed constitutively in many tissues, including the stomach, kidney, and platelets, whereas COX-2 is expressed only at the site of **inflammation** (see, for example, S. Kargan et al. in Gastroenterol., 111:445-454 (1996)). The prostagladins derived from COX-1 are responsible for many. . .
SUMM . . . data, the development of highly selective COX-2 inhibitors appears to be a sound strategy to develop a new generation of anti-**inflammatory** drugs. However, the physiological functions of COX-1 and COX-2 are not always well defined. Thus, there is a possibility that prostagladins produced as a result of COX-1 expression may also contribute to **inflammation**, pain and fever. On the other hand, prostagladins produced by COX-2 have been shown to play important physiological functions, including. . .
SUMM . . . (e.g., dithiocarbamates (DC)) and pharmacologically active agents (e.g., NSAIDs). Invention conjugates provide a new class of pharmacologically active agents (e.g., anti-**inflammatory** agents) which cause a much lower incidence of side-effects due to the protective effects imparted by modifying the pharmacologically active. . .

SUMM . . . It is now recognized that excessive nitric oxide production can induce the expression of COX-2, thereby enhancing the cascade of **inflammatory** reactions. Thus, scavenging NO by a nitric oxide scavenger (such as the dithiocarbamate-iron complex) could reduce the negative consequences brought. . .

SUMM . . . thereby preventing the production of peroxynitrite, a potent oxidant, and reducing the induction of COX-2 expression, which could induce further **inflammatory** response.

SUMM . . . Chem., 267:16323-16329 (1992)). Endothelial expression of VCAM-1 causes the adherence of neutrophils to the endothelium, an early event leading to **inflammation** and subsequent vascular damage and reduction of blood flow (see, for example, M. N. Oppenheimer et al., in J. Immunol.,. . .

SUMM Diseases and conditions contemplated for treatment in accordance with the present invention include **inflammatory** and infectious diseases, such as, for example, septic shock, hemorrhagic shock, anaphylactic shock, toxic shock syndrome, ischemia, cerebral ischemia, administration of cytokines, overexpression of cytokines, ulcers, **inflammatory** bowel disease (e.g., ulcerative colitis or Crohn's disease), diabetes, arthritis, **asthma**, Alzheimer's disease, Parkinson's disease, multiple sclerosis, cirrhosis, allograft rejection, encephalomyelitis, meningitis, pancreatitis, peritonitis, vasculitis, lymphocytic choriomeningitis, glomerulonephritis, uveitis, ileitis, **inflammation** (e.g., liver **inflammation**, renal **inflammation**, and the like), burn, infection (including bacterial, viral, fungal and parasitic infections), hemodialysis, chronic fatigue syndrome, stroke, cancers (e.g., breast,. . . like), cardiopulmonary bypass, ischemic/reperfusion injury, gastritis, adult respiratory distress syndrome, cachexia, myocarditis, autoimmune disorders, eczema, psoriasis, heart failure, heart disease, **atherosclerosis**, dermatitis, urticaria, systemic lupus erythematosus, AIDA, AIDS dementia, chronic neurodegenerative disease, chronic pain, priapism, cystic fibrosis, amyotrophic lateral sclerosis, schizophrenia,. . .

SUMM T cell inhibitors such as synthetic leucocyte antigen derived peptides, **interleukin-1** receptor antagonist, MG/AnergiX, anti-CD3 monoclonal antibodies, anti-CD23 monoclonal antibodies, anti-CD28 antibodies, anti-CD2 monoclonal antibodies, CD4 antagonists, anti-E selectin antibodies, MHC. . .

SUMM . . . TBP-1), cobra venom factor, interleukin 1a agonist (e.g., cytogenin), interleukin 2 receptor antagonist (e.g., dacliximab), ICAM 1 antagonist (e.g., enlimomab), **interleukin 1** beta converting enzyme inhibitors (e.g., ICE-inhibitors), interferons (e.g., thymocartin), interleukin-10, interleukin-13, **interleukin 1** antagonist (e.g., SR-31747 and TJ-114), interleukin-2 antagonist (e.g., sirolimus), phospholipase C inhibitor, neurokinin 1 antagonist (e.g., L-733060), laflunimus, leflunomide, leucotriene. . . cysteine protease inhibitor (e.g., GR-373), metalloproteinase inhibitor (D-5410), lipocortins synthesis agonist (e.g., rimexolone, predonisolone 21-farnesylate, HYC-141, and deflazacort), chelating agent (**diacerein**), elastase inhibitors, DNA directed RNA polymerase inhibitor (e.g., estrogens), oxygen radical formation antagonist (e.g., glucosamine sulfate), thrombin inhibitors (e.g., GS-522),. . .

SUMM . . . (RBE limonene), immunostimulants (e.g., CGP-19835A, lipid A vaccine, edobacomab, nebacumab, StaphGAM, and diabodies), immunosuppressants (e.g., CytoTAB, and transcyclopentanyl purine analogues), **interleukin 1** antagonists (e.g., **interleukin 1** receptors), **interleukin 1** receptor antagonists (e.g., anakinra), interleukin 1b antagonists (e.g., **interleukin-1**.beta.), interleukin

1beta converting enzyme inhibitors (e.g., ICE-inhibitors), interleukin 8
antagonists (e.g., IL-8 receptor), interleukin 13 agonists (e.g., interereleukin-13), ITF-1697, lipase. . .
SUMM multiple sclerosis agents, such as 4-aminopyridine, 15.+-.deoxyspergualin, ACTH, amantadine, antibody adjuvants (e.g., poly-ICLC,
and poly-IC+poly-L-lysine+carboxymethylcellulose), anti-cytokine MAb (CDP-835), anti-**inflammatory** (e.g., CY-1787, and CY-1503), anti-selectin MAb (e.g., CY-1787), anti-TCR MAb (e.g., NBI-114, NBI-115,
and NBI-116), bacloten, bethanechol chloride, carbamazepine, carbohydrate. . .
SUMM . . . 5-LO/CO inhibitors (e.g., BF-397, Tenidap, CP-309, and CP-66248), angiogenesis inhibitors (e.g., platelet factor 4), anticancer
antibiotic (e.g., AGM-1470, and TNP-470), anti-**inflammatory** cytochrome P450 oxidoreductase inhibitors (e.g., DuP-630, and DuP-983), antiproliferative compounds (e.g., Zyn-Linker), arachidonic acid analogues (e.g., CD581, and CD554), arachidonic. . .
SUMM . . . (e.g., Enlimomab), immunosuppressants (e.g., small molecule compounds, and NBI-117), integrin general antagonists (e.g., monoclonal antibody AN-100225, and monoclonal antibody AN-100226), **Interleukin-1** antagonists (e.g., cyclic nitrones), iron-dependent lipid peroxidation inhibitors (e.g., 2-(amino-methyl) chromans), lactic acid accumulation/inhibitors (e.g., small molecule CPC-211), Leukotriene B4. . .
SUMM agents useful for the treatment of carcinomas (e.g., adriamycin, taxol, **interleukin-1**, interleukin-2 (especially useful for treatment of renal carcinoma), and the like, as well as leuprolide acetate, LHRH analogs (such as. . .
DETD Evaluation on the Anti-**Inflammatory** Effects of the Conjugate of Pyrrolidinol Dithiocarbamate and Ibuprofen (PDI)
CLM What is claimed is:
. . . treatment of ischemia/reperfusion injury, agents useful for the treatment of ophthalmic diseases, agents useful for the treatment of cardiovascular diseases, anti-**inflammatory** agents or antioxidants.

AN 1999:72602 USPATFULL|
TI Conjugates of dithiocarbamates with pharmacologically active agents and uses therefore|
IN Lai, Ching-San, Encinitas, CA, United States
PA Medinox, Inc., San Diego, CA, United States (U.S. corporation)
PI US 5916910 19990629 <--
AI US 1997-869158 19970604 (8)
DT Utility|
FS Granted|
EXNAM Primary Examiner: Davis, Zinna Northington|
LREP Reiter, Esq., Stephen E.Gray, Cary, Ware & Freidenrich|
CLMN Number of Claims: 27|
ECL Exemplary Claim: 1|
DRWN No Drawings
LN.CNT 1842|
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L10 ANSWER 5 OF 7 USPATFULL
PI US 5703119 19971230 <--
SUMM . . . pharmaceutically acceptable acid addition salt thereof, together with a pharmaceutically acceptable carrier. The "condition" is meant to include arthritis, e.g., **rheumatoid arthritis** and osteoarthritis, cancer, periodontitis, and **osteoporosis**.
DETD In the case of oral dosing for the treatment or prophylaxis of arthritis
or **inflammation** in general, due to any course, a suitable dose of a compound of Formula I or physiologically acceptable salt thereof,.

. .
DETD **Interleukin-1** has been shown to induce a loss of proteoglycans from cartilage cultures, possibly by stimulating synthesis of the proteoglycan degrading. . .
DETD . . . are important enzymes for the degradation of extracellular matrix components such as collagen and proteoglycans in many disease processes including **rheumatoid arthritis**, osteoarthritis, cancer, periodontitis, and **osteoporosis**. MMPs are also involved in eye diseases such as corneal ulcer formation.
DETD . . . cartilage is obtained from a local slaughter house (Milan, Mich.); cell culture reagents from Gibco (Grand Island, N.Y.); human recombinant **Interleukin-1**.beta. (IL-1.beta.) from Boehringer Mannheim (Indianapolis, Ind.); DMB from Polysciences (Warrington, Pa.); Falcon 24 well flat-bottom tissue culture plates from Becton. . .
DETD . . . aminoprofen, anitrazafen, antrafenine, auranofin, bendazac lysinate, benzydamine, beprozin, broperamole, bufezolac, carprofen, cinmetacin, ciproquazone, clidanac, cloximate, dazidamine, deboxamet, delmetacin, detomidine, dexindoprofen, **diacerein**, di-fisalamine, difenpyramide, emorfazone, enfenamic acid, enolicam, epirizole, etersalate, etodolac, etofenamate, fanetizole mesylate, fenclofenac, fenclorac, fendosal, fenfluminzole, fentiazac, feprazone, floctafenine, flunixin,. . .
AN 97:123255 USPATFULL
TI Benzylidene-lactone derivatives of fenamates and their thiocarbonyl analogs as inhibitors of proteoglycan degradation
IN Baragi, Vijaykumar, Ann Arbor, MI, United States
Boschelli, Diane Harris, Plymouth, MI, United States
Connor, David Thomas, Ann Arbor, MI, United States
Renkiewicz, Richard Raymond, Novi, MI, United States
PA Warner-Lambert Company, Morris Plains, NJ, United States (U.S. corporation)
PI US 5703119 19971230 <--
AI US 1995-448817 19950524 (8)
RLI Division of Ser. No. US 1994-273668, filed on 12 Jul 1994, now abandoned which is a division of Ser. No. US 1993-97356, filed on 26 Jul 1993, now patented, Pat. No. US 5358964
DT Utility
FS Granted
EXNAM Primary Examiner: Fan, Jane
CLMN Number of Claims: 7
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 557
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L10 ANSWER 6 OF 7 USPATFULL
PI US 5627173 19970506 <--
AB . . . producing pharmaceuticals for the treatment and prophylaxis of degenerative joint disorders, of rheumatic disorders accompanied by cartilage breakdown, such as **rheumatoid arthritis**, joint trauma and chondrolysis as a consequence of prolonged immobilization of the joint, of **inflammations**, septic shock, disorders with impaired leukocyte adhesion, disorders caused by an elevated concentration of tumor necrosis factor alpha, such as. . .
SUMM Osteoarthritis is a degenerative joint disorder with **inflammatory** episodes and progressive cartilage dysfunction which may lead to impairment of function or even complete ankylosis. Although to date the concomitant **inflammations** and states of pain associated with this disorder can be treated, there are no available pharmaceuticals which have been proven. . . of known therapeutic agents for osteoarthritis are mixtures of sulfated

glucosaminoglycans (Current Therapeutic Research, 40, 6 (1986) 1034) or non-steroidal anti-**inflammatory** drugs, but these are unable to stop the loss of cartilage. Although the pathogenesis of osteoarthritis and arthritis has not. . .

SUMM . . . suitable for the treatment and prophylaxis of degenerative joint disorders, of rheumatic disorders accompanied by cartilage breakdown, such as chronic **rheumatoid arthritis**, joint trauma and chondrolysis as a consequence of prolonged immobilization of the joint, of **inflammations**, septic shock, disorders with impaired leukocyte adhesion, disorders caused by an elevated concentration of tumor necrosis factor alpha, such as. . .

SUMM Examples of degenerative joint disorders are osteoarthritis, other rheumatic disorders with cartilage breakdown, **rheumatoid arthritis**, chondrolysis after joint trauma, for example, after meniscus or patella injuries or torn ligaments, or chondrolysis associated with prolonged immobilization. . .

DETD . . . thereof by the effect of the substance, and equal to 1 when matrix synthesis was unaltered. The standard used was **diacerein** which is used as an osteoarthritis remedy in Italy under the proprietary name Artrodar.

DETD TABLE 2

Effect on IL-I-induced chondrolysis in agarose culture

Example No.	Proteoglycan synthesis stimulation factor
Standard (**diacerein**)	1.1
10	3.5
12	4.1
13	3.3
14	3.8
15	3.4
21	1.3
24	1.6
25	2.1
26	2.1
27	1.9
28	3.0
29	3.4
35	1.3
39	1.2
40	1.2
41	1.2
47	2.4
49	1.4
50	1.4

51. . .

DETD Inhibition of release of **interleukin-1**.beta.: 230 .mu.l of mononuclear cells were incubated with 10 .mu.l of test substance (10 .mu.M in dimethyl sulfoxide (DMSO)/water=1/10) and. . .

CLM What is claimed is:

30. A method for the treatment of degenerative joint disorders, of rheumatic disorders accompanied by cartilage breakdown, of **inflammations**, septic shock, disorders accompanied by impaired leukocyte adhesion, or disorders caused by an elevated concentration of tumor necrosis factor alpha,. . .

31. The method according to claim 30, wherein the rheumatic disorder accompanied by cartilage breakdown is **rheumatoid arthritis**, joint trauma, or chondrolysis resulting from prolonged immobilization.

AN 97:38516 USPATFULL

TI Phosphonoacetic acid derivatives and their use for treating degenerative

joint disorders|
IN Graeve, Rolf, Taunustein, Germany, Federal Republic of
Thorwart, Werner, Hochheim, Germany, Federal Republic of
Raiss, Ruth, Frankfurt, Germany, Federal Republic of
Weithmann, Klaus U., Hofheim, Germany, Federal Republic of
M ullner, Stefan, Hochheim, Germany, Federal Republic of
PA Hoechst Aktiengesellschaft, Frankfurt am Main, Germany, Federal Republic
of (non-U.S. corporation)
PI US 5627173 19970506 <--
AI US 1996-590300 19960123 (8)
PRAI DE 1995-19502209 19950125
DT Utility|
FS Granted|
EXNAM Primary Examiner: Richter, Johann; Assistant Examiner: Ambrose, Michael G.|
LREP Finnegan, Henderson, Farabow, Garrett & Dunner, L.L.P.|
CLMN Number of Claims: 32|
ECL Exemplary Claim: 1|
DRWN No Drawings
LN.CNT 1962|
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L10 ANSWER 7 OF 7 USPATFULL
PI US 5358964 19941025 <--
SUMM . . . pharmaceutically acceptable acid addition salt thereof, together with a pharmaceutically acceptable carrier. The "condition" is meant to include arthritis, e.g., **rheumatoid arthritis** and osteoarthritis, cancer, periodontitis, and **osteoporosis**.
SUMM In the case of oral dosing for the treatment or prophylaxis of arthritis or **inflammation** in general, due to any course, a suitable dose of a compound of Formula I or physiologically acceptable salt thereof,. . .
SUMM **Interleukin-1** has been shown to induce a loss of proteoglycans from cartilage cultures, possibly by stimulating synthesis of the proteoglycan degrading. . .
SUMM . . . are important enzymes for the degradation of extracellular matrix components such as collagen and proteoglycans in many disease processes including **rheumatoid arthritis**, osteoarthritis, cancer, periodontitis, and **osteoporosis**. MMPs are also involved in eye diseases such as corneal ulcer formation.
SUMM . . . cartilage is obtained from a local slaughter house (Milan, Mich.); cell culture reagents from Gibco (Grand Island, N.Y.); human recombinant **Interleukin-1**.beta. (IL-1.beta.) from Boehringer Mannheim (Indianapolis, Ind.); DMB from Polysciences (Warrington, Pa.); Falcon 24 well flat-bottom tissue culture plates from Becton. . .
SUMM . . . aminoprofen, anitrazafen, antrafenine, auranofin, bendazac lysinate, benzydamine, beprozin, broperamole, bufezolac, carprofen, cinmetacin, ciproquazone, clidanac, cloximate, dazidamine, deboxamet, delmetacin, detomidine, dexindoprofen, **diacerein**, di-fisalamine, difenpyramide, emorfazone, enfenamic acid, enolicam, epirizole, etersalate, etodolac, etofenamate, fanetizole mesylate, fenclofenac, fenclorac, fendosal, fenfluminzole, fentiazac, feprazone, floctafenine, flunixin,. . .
AN 94:93343 USPATFULL
TI Benzylidene-lactone and their thiocarbonyl analogs as inhibitors of proteoglycan degradation
IN Baragi, Vijaykumar, Ann Arbor, MI, United States
Boschelli, Diane H., Plymouth, MI, United States
Connor, David T., Ann Arbor, MI, United States
Renkiewicz, Richard R., Novi, MI, United States
PA Warner-Lambert Company, Morris Plains, NJ, United States (U.S.

corporation)
PI US 5358964 19941025 <--
AI US 1993-97356 19930726 (8)
DT Utility
FS Granted
EXNAM Primary Examiner: Fan, Jane T.
LREP Daignault, Ronald A., Ashbrook, Charles W.
CLMN Number of Claims: 11
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 542
CAS INDEXING IS AVAILABLE FOR THIS PATENT.